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Reactivity and Conformation of Systems containing a Three-membered Heterocycle Conjugated with an Unsaturated Group

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Steroidal epoxides, aziridines, and episulphides containing a vicinal unsaturated group (ketone or hydrazone) are used as examples to examine, systematise, and generalise reactions involving nucleophilic opening of a three-membered ring. The influence of an adjacent substituent on the structural and stereochemical trends of such reactions is discussed. A list of 107 references is included.

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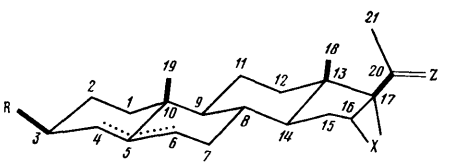
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I. INTRODUCTION

The many reviews covering epoxides[1-5], aziridines[6,7], and episulphides[8,9] devote only insignificant space to the reactions of three-membered heterocycles conjugated with keto or other unsaturated group[1,7]. Often the general principles of the chemistry of three-membered rings cannot be used to foretell the direction of ring-opening in such systems, and it is difficult to predict and explain the results of reactions in any particular case[10]. Even in the relatively well-studied field of keto-epoxides definite correlations have not been established between substrate structure, reagent, and the conditions and direction of reactions: several views are held on the mechanism which best describes such reactions[3,10,11]. It may be supposed *a priori* that the direction of ring-opening will be determined by the concerted (or competing) influence of the nature of the heterocycle, the adjacent unsaturated group, and their relative arrangement (interaction). However, to determine the role of each of these factors in studying conformationally labile systems such as aliphatic epoxy(or epi-imino)-ketones is an almost hopeless task.

In fact the nature of the electronic interactions between three-membered ring (epoxy, epi-imino, cyclopropyl)† and neighbouring carbonyl group is usually described as conjugation resulting from orbital overlap of banana bonds of the ring and a *p*-orbital of the carbonyl group[12-14]. After Walsh had predicted[13] the geometrical requirements for such interaction, Cromwell[12] showed that maximum conjugation in such systems is achieved with the planes of carbonyl group and three-membered ring parallel and the keto-group on a bisector of the ring. Therefore the problem of reactivity and direction of ring-opening must, of course, be considered in connection with the conformation of the adjacent portion of the molecule.

The present Review represents an attempt to systematise scission reactions of three-membered rings with steroids as conformationally rigid models, in which the side-chain containing the unsaturated group adjacent to the three-membered ring is capable of rotating about the $C_{(17)}-C_{(20)}$ bond:



β-region (front) of molecule

X=O, NH, NAc, S Z=O, $NNHCO_2C_2H_5$ R=OH, OAc, Δ^5; O, Δ^4

α-region (rear) of molecule

Because of structural and electronic features, however, the barrier to rotation is quite high, and the molecule is fixed in one of the preferred conformations depending on the nature of the heterocycle and its immediate environment[15-17]. This enables the relative influence of the above factors on reactivity and direction of reaction to be traced from stereochemically reliable data on ring-opening in such systems.

II. RING-OPENING IN EPIMERIC 16,17-EPOXY-20-OXO-STEROIDS

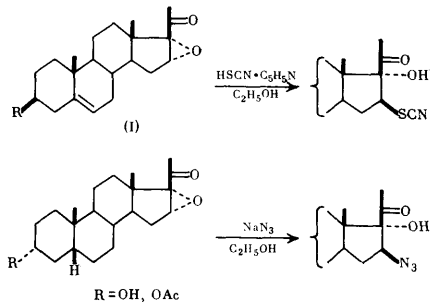
Among the 16,17-hetero-substituted 20-keto-steroids discussed only the epoxy-ketones have been widely studied; they showed clearly that the structural and stereochemical direction of ring-opening depends on the structure of the oxide, the nature of the reagent, and the reaction conditions. Most of the reactions studied are examples of acid-catalysed nucleophilic ring-opening. Exceptions are provided by the scission of 16,17-epoxy-20-ketones by highly nucleophilic reagents and by their aminolysis, which we shall consider first. In the former case solvation of the oxide ring by protons of the solvent provides electrophilic assistance to scission, and in the latter case the reagent itself acts as an alkaline catalyst.

1. Ring-opening under Neutral Conditions and Aminolysis

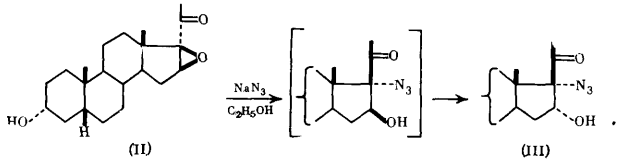
In neutral media 16,17α-epoxy-20-oxo-steroids (I) undergo exclusively *trans*-opening of the oxide ring at the more

†Episulphides containing a vicinal unsaturated group have not hitherto been studied.

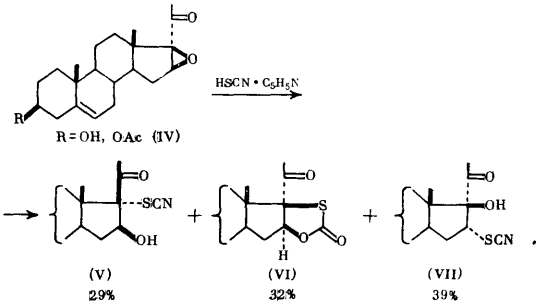
substituted carbon atom[18-20]:



A protic solvent undoubtedly helps to increase the reaction velocity, for in an aprotic medium the reaction, e.g. with thiocyanic acid, does not take place[19]. The analogous reactions of 16,17β-epoxy-20-oxo-steroids occur with the opposite structural selectivity. The only product of azidolysis of the 16,17β-epoxide (II) under identical conditions is that of attack by the azide ion at the tertiary atom with Walden inversion, epimerisation at the $C_{(16)}$ atom being regarded[20] as a secondary process:



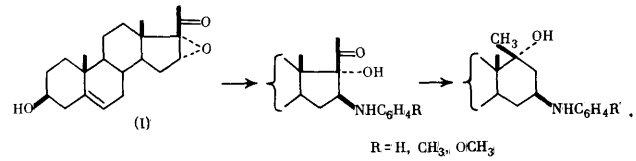
Reaction of the 16,17β-epoxide (IV) with thiocyanic acid is not so selective[21,22]. The tendency to preferential but not exclusive attack at the tertiary centre is maintained. However, both *trans*- and *cis*-scission products (V) and (VI) are formed, with a total yield of 60–65%:[21]



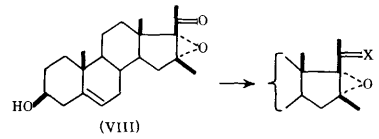
Attack at the secondary atom with formation of the *trans*-hydroxy-thiocyanate (VII) takes place to a lesser but appreciable extent (~40%).

These results on the scission of 16,17β-epoxy-20-oxo-steroids by thiocyanic and hydrazoic acids, at first glance contradictory, become consistent on the assumption that formation of the 17α-azide (III) is a consequence of a retroaldol type of epimerisation[23] not of one, as had been assumed[20], but of two 17-azides, with α- and β-configurations of the azide function, formed in the reaction medium. Such epimerisation is, of course, completed by stabilisation of the thermodynamically more stable isomer (III) having β-orientation of the 17-acetyl group.

No information has been published on the aminolysis of 16,17β-epoxy-20-oxo-steroids, while results on the structure and configuration of products obtained with ring-opening of their 16,17α-epimers by amines are very few and contradictory[24]. A critical approach must be adopted to most of the early literature, mainly patents, with reference to the formation of 16-amino-17α-hydroxy-20-oxo-steroids on reaction with primary and secondary amines[25-27], since structures were assigned to the products without evidence. According to Frangulyan et al.[24,28,29] opening of the oxide ring of 16,17α-epoxy-20-oxo-steroids by aromatic amines (aniline, *p*-toluidine, *p*-anisidine) takes place with D-homoisomerisation, which implies initial formation of 16β-amino-17α-hydroxypregnanes, attempts to isolate which proved unsuccessful:



Even these few results show that, in the ring-opening of 16,17α-epoxy-ketones by bases, attack by the nucleophile is directed at the secondary centre, the β-position. When such attack is sterically hindered, as e.g. in the action of ammonia or a primary amine on the 16,17α-epoxy-16β-methyl-ketone (VIII), reaction takes place at the 20-oxo-group with elimination of water and without involving the oxide ring[30]:



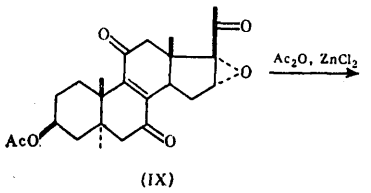
X = NH, NCH_3, *n*-C_6H_9N, $N(CH_2)_2NH_2$, $N(CH_2)_2OH$, *N*-C_8H_9N .

2. Acid-catalysed Ring-opening of Epimeric 16,17-Epoxy-20-oxo-steroids

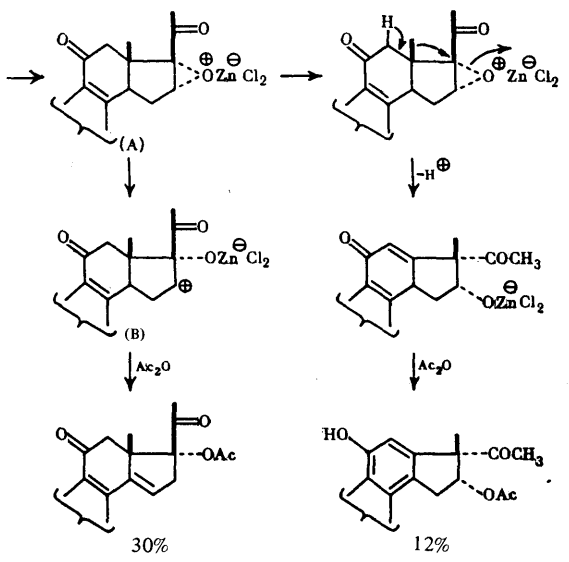
Reactions of this type include the ring-opening of 16,17-epoxy-20-oxo-steroids by hydrohalic acids (below) and the addition of water, acetic acid, methanol, thioacetic acid, hydrazoic acid, and other reagents catalysed by mineral or Lewis acids. They have been referred to many times in the literature, but with few exceptions the complete pattern of structural and steric trends has not been studied. The present Review is confined to published results, including a complete analysis of the reaction mixture. Protonation of the oxide ring or coordination with a Lewis acid is a necessary stage in these processes[3]. The direction of opening of the oxide ring depends both on the structure and stereochemistry of the initial oxide and on the nucleophilicity of the reagent.

In the acid-catalysed ring-opening of 16,17α-epoxy-20-oxo-steroids the tendency of the oxide to break at the tertiary centre closest to the keto-group increases in proportion to the decrease in nucleophilicity of the reagent. Incorporation of the nucleophile at the $C_{(17)}$ atom is observed only in exceptional cases and to an extremely insignificant extent. Stabilisation of the positive centre formed is usually completed by 1,2-migration of the angular methyl group. Thus in reactions of this type with weak nucleophiles or in their absence intermediate products are stabilised by rearrangements involving rupture mainly of the $C_{(17)}$–O and to a less extent the $C_{(16)}$–O bond[31], with the quantity of open-chain products apparently measuring the stability of the intermediates. A reaction of interest from

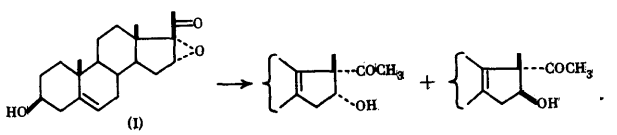
this point of view is that of the 16,17α-epoxide (IX) with acetic anhydride catalysed by zinc chloride[32], regarded as taking place by two competing routes, one of which involves a Wagner–Meerwein rearrangement by a synchronous mechanism with elimination of a proton from $C_{(12)}$ followed by enolisation and replacement of zinc chloride by an acylium ion:



(IX)

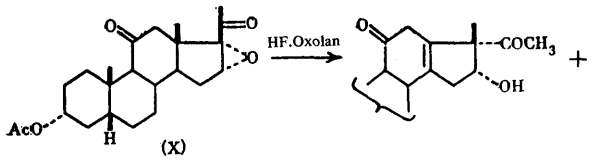


The alternative ring-opening of the intermediate A will give the 16-carbocation B, which is stabilised with elimination of a proton from the $C_{(15)}$ atom followed by allyl rearrangement of the $\Delta^{15,16}$ bond to a conjugated position. Apparently the relative contents of products formed with rupture of the $C_{(17)}$–O or $C_{(16)}$–O bond in reactions of this type depend to a considerable extent on the structure of the initial oxide and the catalyst used. Thus hydrolysis of the 16,17α-epoxide (I) in methanol catalysed by perchloric or sulphuric acid is 75–80% accompanied by a Wagner–Meerwein rearrangement with formation of an equilibrium mixture of epimers at the $C_{(16)}$ atom[33]:

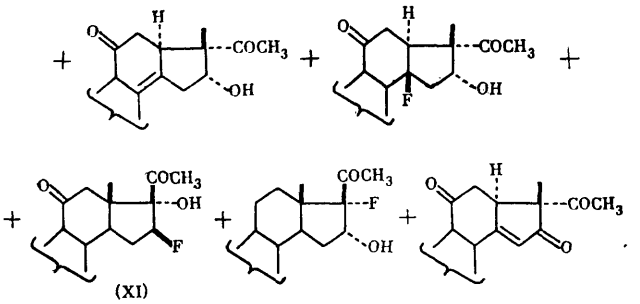


(I)

A similar structural trend is exhibited by the action of hydrogen fluoride on the epoxide (X), which differs from the reactions with hydriodic and hydrobromic acids[34–36] in involving rupture of the $C_{(17)}$–O bond and is usually completed by migration of the angular methyl group[37]; the expected *trans*-fluorohydrin (XI) is formed in only 2% yield:



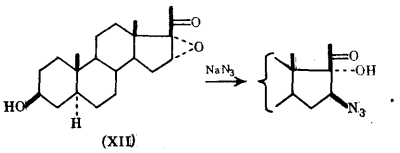
(X)



(XI)

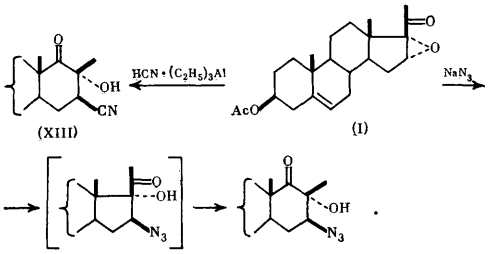
Ring-opening of 16,17α-epoxy-ketones with hydrobromic or hydriodic acid, which is most widely used in practice, is reported as yielding 30–70% of *trans*-products with rupture of the $C_{(16)}$–O bond and incorporation of the halogen at this position[34–36].

The acid-catalysed reactions of 16,17α-epoxy-20-oxo-steroids with such strongly nucleophilic reagents as e.g. azide and cyanide ions exhibit high stereo- and regio-selectivity. The course of the reaction of the epoxide (XII) with sodium azide in dimethyl sulphoxide (DMSO) catalysed by sulphuric acid is identical[38] with that described above in ethanol:



(XII)

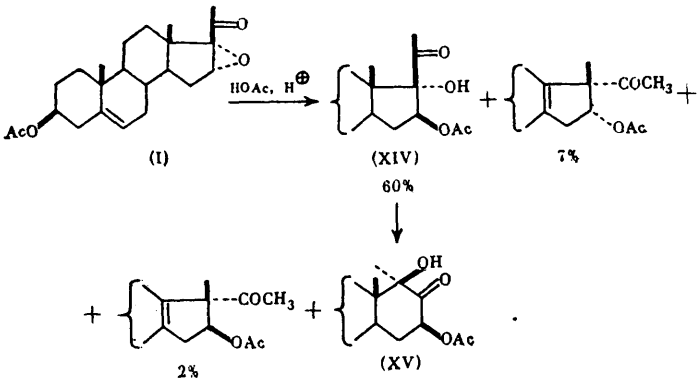
The same reaction is reproduced under identical conditions by the epoxide (I),[39] but a D-homostructure is attributed to the final product. It must be assumed that the absence of D-homoisomerisation in the preceding case is due to the greater stability of the D-ring in 5α-steroids. A similar result has been reported for scission of epoxide (I) by the hydrogen cyanide–triethylaluminium complex[40]; formation of the D-homoketone (XIII) is not unexpected, because of the Lewis nature of the reagent:



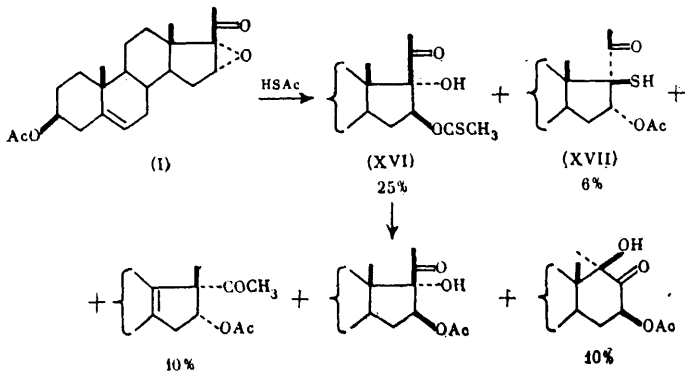
(XIII) (I)

Acetic and thioacetic acids, which are quite strong nucleophiles but considerably weaker than hydrazoic, thiocyanic, hydrobromic, and hydriodic acids, react with the oxide ring

of 16,17α-epoxy-20-oxo-steroids only in the presence of a mineral acid as catalyst. Such reactions are characterised not only by preferential *trans*-opening of the oxide at the secondary centre but also by rupture of the $C_{(17)}$–O bond[41,42]. The main direction in which 16,17α-epoxides are opened by acetic acid is *trans*-attack at the $C_{(16)}$ atom with formation of the 16β-acetate (XIV), which apparently isomerises into the D-homoketone (XV):[41]



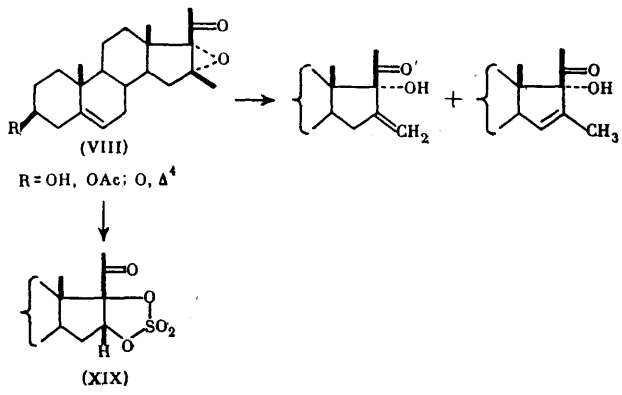
Rupture of the $C_{(17)}$–O bond followed by a Wagner–Meerwein rearrangement is observed to a considerably less extent. Such is the general direction in which the oxide (I) reacts with thioacetic acid in the presence of an inhibitor of free-radical addition and sulphuric acid as catalyst[42]. Thioacetic acid, which reacts in the *O*-form, attacks the $C_{(16)}$ atom to form the 16-*O*-thioacetate (XVI), which under the reaction conditions hydrolyses to the diacetate (XVIII):



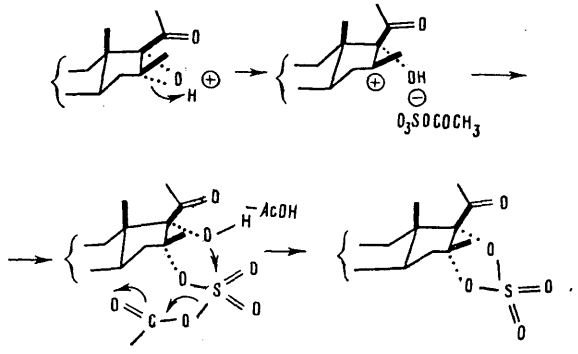
A feature of the reaction is formation of the 17β-thiol (XVII), formally a product of *trans*-opening of the oxide by hydrogen sulphide with attack at the tertiary carbon atom. It must not be forgotten, however, that hydrogen sulphide ions are able to add to a carbonyl group[3,43], so that an alternative possibility is addition to the keto-group of hydrogen sulphide formed by decomposition of thioacetic acid, followed by intramolecular attack at the $C_{(17)}$ atom.

In the ring-opening of 16,17α-epoxy-16β-methyl-20-oxo-steroids by acidic reagents, in contrast to desmethyl oxides, incorporation of the nucleophilic reagent is not usually observed: reactions are completed by formation of unsaturated alcohols, the proportions of which vary with the reaction conditions (reagent, solvent), their formation being regarded as resulting from stabilisation of the $C_{(16)}$ carbocation by elimination of one of the neighbouring protons[44,45]. The direction of stabilisation is largely determined by the possibility of solvation of the 16-centre.

An extremely interesting reaction is the production of 16α,17α-cyclosulphates (XIX) in the ring-opening of the 16β-methyl oxide (VIII) by oleum in glacial acetic acid or by a mixture of acetic anhydride and sulphuric acid in acetic acid, formally involving *cis*-opening of the oxide ring and addition of sulphur trioxide[46]:



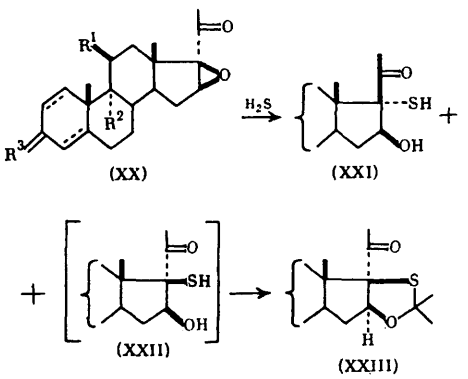
The postulated mechanism involves rupture of the $C_{(16)}$–O bond in the protonated form of the oxide by acetylsulphuric acid, apparently formed by interaction of acetic anhydride with sulphuric acid. Because of steric hindrance by the 13-methyl group, approach of the acetylsulphate ion to the $C_{(16)}$ atom takes place preferentially from the rear of the molecule:



Intramolecular acylation of the free hydroxy-group of the mixed anhydride of sulphuric and acetic acids is assumed to take place in the intermediate product, with formation of a cyclic sulphate[44]. The ease of such transesterification is explained by the close approach of the vicinal *cis*-substituents in the five-membered ring, and bears an analogy to the well-known 17 → 16 acyl migration[1].

The structural direction of ring-opening in 16,17β-epoxy-ketones is less influenced by the reaction conditions: all the reported acid-catalysed reactions occur regiospecifically with rupture of the carbon–oxygen bond at the tertiary carbon atom closest to the carbonyl group. The subsequent behaviour of the resulting intermediate, however, depends to a considerable extent on the conditions: use of an acid catalyst and weakening of the nucleophilicity of the reagent favour isomerisation involving the $C_{(17)}$ centre. On interaction with strongly nucleophilic reagents such as hydrazoic acid[20,38,47], hydrobromic acid[48,49], and hydrogen sulphide[22,50] stabilisation of this centre is effected solely by addition of the nucleophilic species. *trans*-Opening of the oxide at the $C_{(17)}$ atom with incorporation of the nucleophile from the

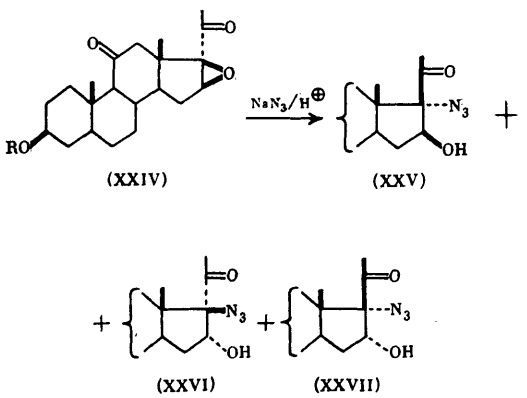
rear of the molecule is the preferred but not exclusive direction of the reactions of 16,17β-epoxy-ketones, for which addition of the nucleophile at the $C_{(17)}$ atom from the β-region is also very characteristic. The stereochemistry of opening of the epoxide ring in (XX) with hydrogen sulphide and sodium azide is interesting. In the reaction of the epoxide with hydrogen sulphide in acetic acid catalysed by toluene-*p*-sulphonic acid the preferred product of *trans*-opening—the thiol (XXI)—is accompanied[22,50] by the *cis*-16,17β-isomer (XXII), identified as the acetonide (XXIII):



(XX) (XXI) (XXII) (XXIII)

R^1 = H, OH, OAc ;
R^2 = H, F ;
R^3 = O, β-OAc, $\Delta^{1,4}$, Δ^4, Δ^5.

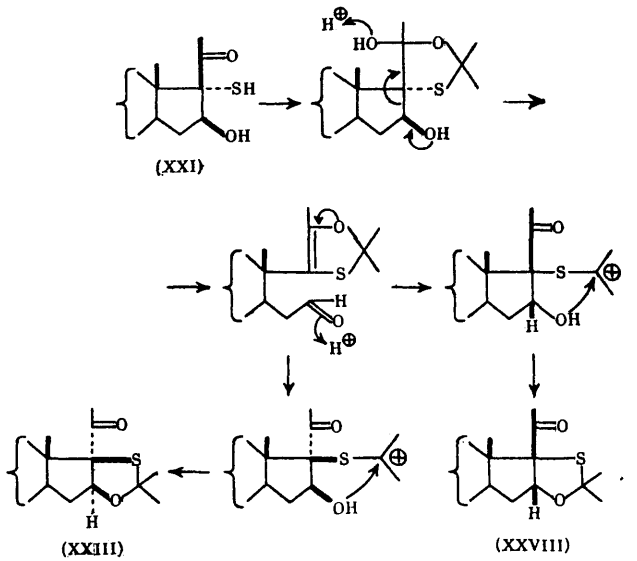
Reaction of the epoxide (XXIV) with sodium azide in the presence of sulphuric acid in DMSO involves formation of the three epimeric azides (XXV)–(XXVII), the proportion of the 16,17α-isomer (XXVII) increasing with the duration of reaction[38]:



(XXIV) (XXV) (XXVI) (XXVII)

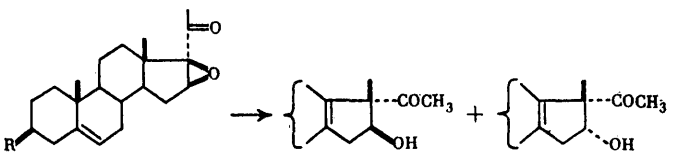
R = H, Ac .

The view[22,37] that a 17α-azido(or mercapto)-16β-ol is formed initially, and isomerises under the reaction conditions by a retroaldol mechanism, is supported by experiment. Thus the *trans*-thiol (XXI) condenses with acetone in the presence of an acid to give the oxathiolan (XXVIII) and its epimer (XXIII), whose formation can be represented



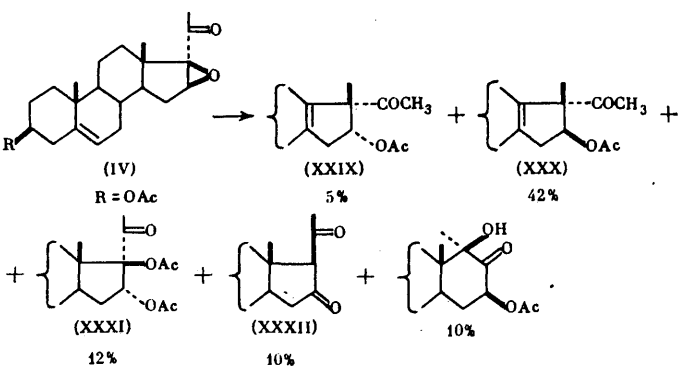
(XXI) (XXIII) (XXVIII)

Nevertheless, these results do not exclude the possibility of direct attack by the hydrogen sulphide or the azide ion from the front of the molecule at the $C_{(17)}$ atom. The tendency for the oxide ring to open at this atom from the β-region in the acid-catalysed reactions of 16,17β-epoxy-20-oxo-steroids is especially clearly evident in the hydrolysis of the epoxide (IV), which occurs solely with migration of the angular methyl group[33]:



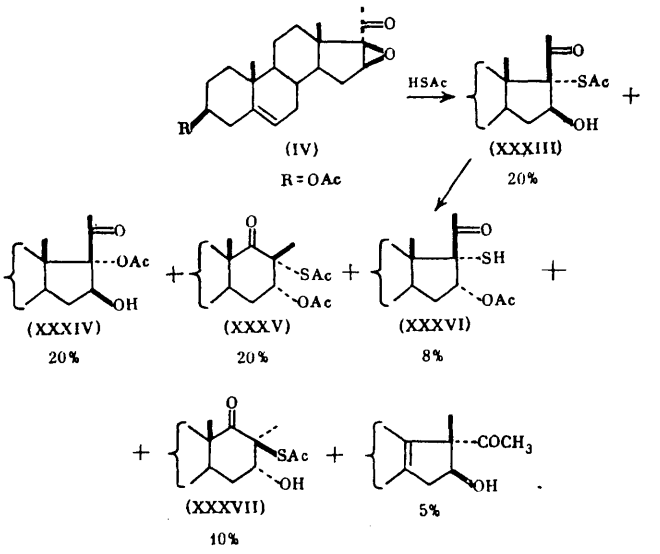
(IV)
R = OH .

Such a structural trend is maintained in the acetolysis of the β-epoxide (IV), when Wagner–Meerwein rearrangement products (XXIX) and (XXX) are accompanied by the *trans*-diacetate (XXXI), formation of this last compound being observed by attacking with the acetate ion from the β-region to neutralise the 17-carbocation and then epimerising and acetylating at $C_{(16)}$:[33]



(IV) (XXIX) (XXX) (XXXI) (XXXII)
R = OAc 5% 42% 12% 10% 10%

The *S*-thioacetate (*O*-thioacetate) ion is more nucleophilic than acetate, which influences the action of thioacetic acid on the β-epoxide (IV), when incorporation of the nucleophile at the $C_{(17)}$ atom from the rear of the molecule is the main route[51,52]. The *cis*-isomer (XXXVI) is a secondary product of epimerisation of the 17α-*S*-thioacetate (XXXIII) formed initially, while the 17α-acetate (XXXIV) is a secondary product of hydrolysis of the 17α-*O*-thioacetate formed in the reaction:

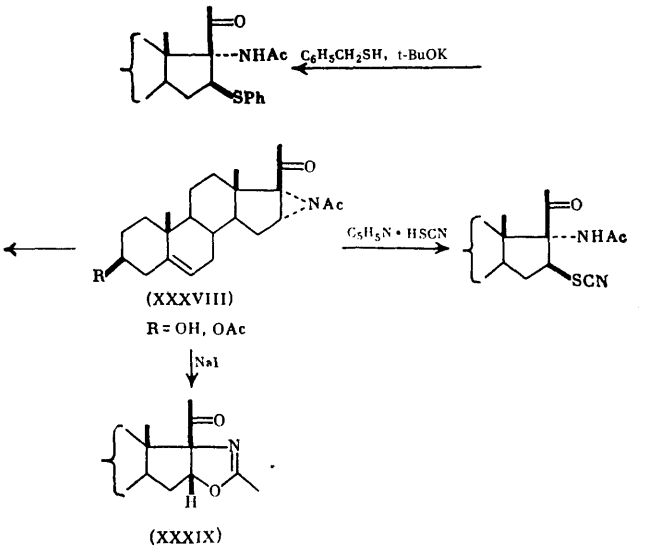


Formation of the D-homoisomers (XXXV) and (XXXVII) is apparently a consequence of D-homoannelation of the primary products of ring-opening.

III. OPENING OF THE AZIRIDINE RING IN 16,17α-EPI-IMINO-20-OXO-STEROIDS AND THEIR *N*-ACETATES

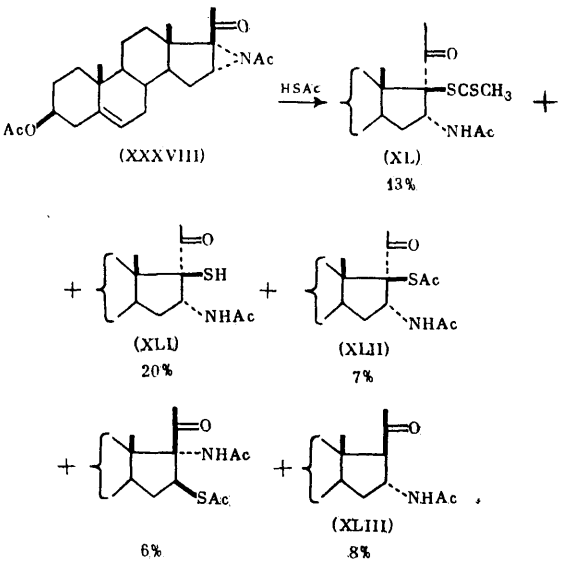
The chemistry of 16,17-epi-imino-20-oxo-steroids has not been developed so actively as that of the 16,17-epoxy-derivatives. Of the two epimeric 16,17ξ-epi-imino-ketones only the 16,17α-isomer has been prepared for study of its ring-opening reactions[53–59]. Existing results indicate firstly low reactivity not only of basic (NH) but also of activated# aziridines in ring-opening and secondly an enhanced tendency for the 20-oxo-group to undergo nucleophilic addition. Thus 16,17α-epi-imino-20-oxo-steroids and their *N*-acetates are inert under conditions under which the corresponding epoxides undergo ring-opening (under the influence of water, hydrazoic acid, acetic acid, methanol), and do not react with potassium thiocyanate in acetic acid[58]; under more severe conditions, in particular catalysis by mineral acids, a Wagner–Meerwein rearrangement takes place exclusively. 16,17α-Acetylepi-imines react only with such nucleophilic reagents as benzenethiol[65,56], pyridine–thiocyanic acid[58], and sodium iodide[57].

These reactions occur by paths characteristic of bio-molecular nucleophilic substitution with rupture solely of the $C_{(16)}$–N bond with inversion of configuration at this centre:



Formation of the 2′-methyl-[16,17α-*d*]oxazoline (XXXIX) by the action of sodium iodide on (XXXVIII) [39] must apparently be regarded as involving double Walden inversion–initial attack by the iodide ion at the $C_{(16)}$ atom followed by intra-molecular substitution of iodine by an internal nucleophile from the rear of the molecule.

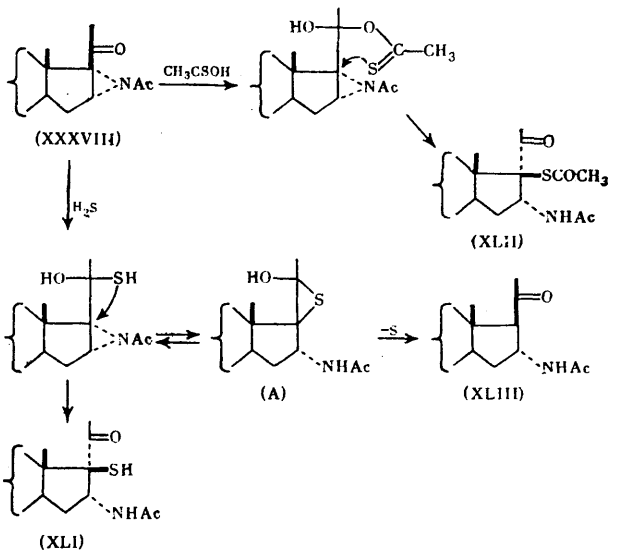
The course of reaction of the *N*-acetylepi-imine (XXXVIII) with thioacetic acid contradicts the general rule of orientation, and leads to preferential rupture of the tertiary $C_{(17)}$–N bond:



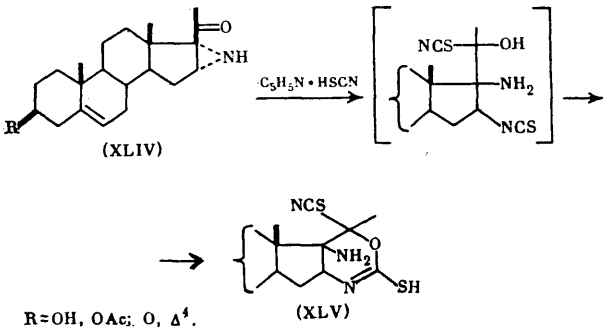
It could be included formally among acid-catalysed reactions of activated aziridines, which take place exclusively (above) with rupture of the $C_{(17)}$–N bond, completed by a Wagner–Meerwein rearrangement. Stabilisation of the $C_{(17)}$ centre should then lead not only to *trans*-addition of the *S*-acetate ion but also to migration of the angular methyl group, which has not been observed. The most acceptable explanation of the observed anomaly[59] is that the largest partial positive charge in the *N*-acetylepi-imine molecule (XXXVIII) is localised on the carbonyl $C_{(20)}$ atom, and this with the

#Activated aziridines have a substituent attached to the nitrogen atom, capable of stabilising the negative charge formed on the nitrogen in the transition state when the compound reacts with a nucleophile[6].

general inertness of the molecule creates favourable conditions for nucleophilic attack on this centre, the reactive species being thioacetatic either *S*- or *O*-acid:

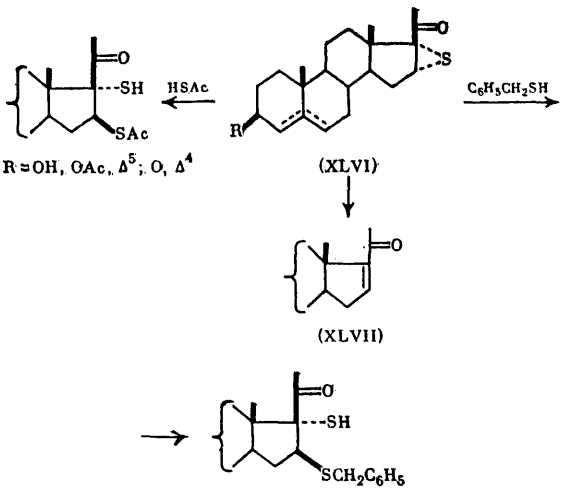


Subsequent intramolecular attack on the $C_{(17)}$ atom with synchronous rupture of the $C_{(17)}$–N bond is assumed to yield the amides (XLI) and (XLII), the former being acylated under the reaction conditions by thioacetic *O*-acid to give (XL). In terms of this scheme formation of the amide (XLIII) was regarded as involving the intermediate episulphide (A), which is desulphurised under acid conditions. This mechanism is consistent with the above tendency of hydrogen sulphide to add to the carbonyl group in epoxy-ketones[3] and also with that of thiocyanic acid to attack the keto-group in 16,17α-epi-imines (XLIV) to form (XLV) [60]



IV. REACTIVITY AND DIRECTION OF RING-OPENING IN 16,17α-EPITHIO-20-OXO-STEROIDS

Epithio-ketones as a class have remained almost unstudied, and no data on physicochemical properties or chemical behaviour are available other than those obtained for 16,17α-epithio-keto-steroids obtained in the Reviewers' laboratory[61,62]. 16,17α-Episulphides are intermediate in reactivity[22,61] between the corresponding oxygen and nitrogen compounds. They are inert under conditions under which the corresponding 16,17α-epoxides undergo ring-opening by such reagents as acetic, thiocyanic, and hydrazoic acids and methanol[62]. Raising the temperature or increasing the duration of reaction leads to elimination of sulphur with formation of the enone (XLVII) and subsequent addition of the nucleophilic reagent to the resulting double bond:



An exception is provided by the reactions of the episulphide (XLVI) with thioacetic acid and with phenylmethanethiol, which involve *trans*-opening of the ring at the less substituted atom $C_{(16)}$. Nucleophilic desulphurisation of the episulphide (XLVI) competes with nucleophilic ring-opening and in most cases predominates. Several aspects must be noted: (*a*) catalysis by a mineral acid (hence protonation of the episulphide ring) is not a necessary condition for elimination reactions [in a weak nucleophile—methanol, acetic acid—the epithio-ketone (XLVI) is stable in the presence of a mineral acid at 20 °C]; (*b*) the presence in the reaction medium of a strong nucleophile promotes desulphurisation even in the absence of a mineral acid (potassium thiocyanate in ethanol at ~80 °C); and (*c*) desulphurisation is equally promoted by a base. In contrast to epoxy(and epi-imino)-ketones the isomeric epithio-ketones (XLVI) apparently do not undergo reactions involving rupture of the $C_{(17)}$–S bond with stabilisation of the resulting electrophilic centre by 1,2-migration of the angular methyl group. If this bond is broken, the molecule is most probably stabilised by elimination of sulphur.

V. INVOLVEMENT OF A HYDRAZONE GROUP IN RING-OPENING IN 16,17-EPOXY(EPI-IMINO, EPITHIO)-20-OXO-STEROIDS

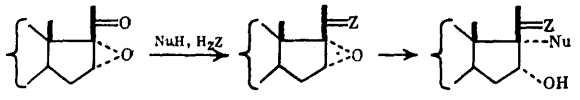
Replacing a keto-group by a hydrazone fragment increases markedly the reactivity of α-substituted ketones in elimination and substitution reactions, in which configuration is usually maintained[63]. This property of hydrazones has been thoroughly studied from both practical and theoretical points of view in a series of investigations undertaken in the Reviewers' laboratory on the involvement of the hydrazone fragment in opening the oxide[64–84], epi-imino[85–95], and episulphide[62,96] rings of 16,17-epoxy(epi-imino, epithio)-20-oxo-steroids. The resulting generalisations have been applied to the controlled modification of steroidal compounds. The stereochemical aspect and the mechanism have been studied in detail on 16,17-epoxy-ketones, with examination of the influence of the stereochemistry of the initial oxide on the stereochemical direction

in which the oxide ring is opened by nucleophilic reagents[63,97].

1. Epimeric 16,17ξ-Epoxy-20-oxo-steroids

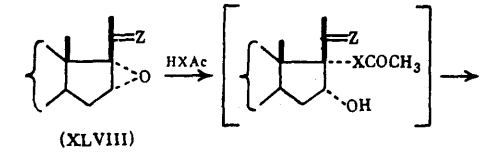
The presence of a reagent for the carbonyl group (a hydrazine) produces a marked change in the direction of ring-opening in 16,17-epoxy-ketones. In all cases regio-specific *cis*-opening of the ring is observed at the position closest to the hydrazone group; the general reactivity of the system towards ring-opening reactions is appreciably enhanced. Hydrazine plays a direct part in the reactions, adding to the keto-group by the stage preceding ring-opening[75,81,83] and forming the 20-hydrazone of the corresponding oxide[64,76-78]. With the above general structural direction of opening in 20-hydrazones of epimeric 16,17α-epoxy-ketones the final result is different and depends solely on the stereochemistry of the oxide ring.

The general scheme of ring-opening in 16,17α-epoxides in the presence of ethyl hydrazine carboxylate is

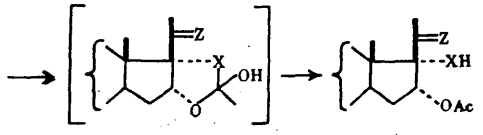


Nu = OH[65], OCH_3[67], OAc[64], SAc[71, 72], N_3[68-70], SCN[73, 74]
$Z = NNHCO_2C_2H_5$

where the reagents used for this purpose are enumerated. All the reactions take place stereo- and regio-specifically with *cis*-opening of the oxide ring at the tertiary carbon atom and incorporation of the reagent from the rear of the molecule. The *cis*-position of the resulting vicinal group quite often favours secondary cyclisation involving these substituents, a particular case of which is acyl migration. Thus reaction of the epoxide (I) with acetic and thioacetic acids under conditions of *cis*-opening[64,71,72] yields the 17α-hydroxy(or mercapto)-16α-acetates (XLIX) or (L), formed by the well-known route[97] via the orthoester intermediate:

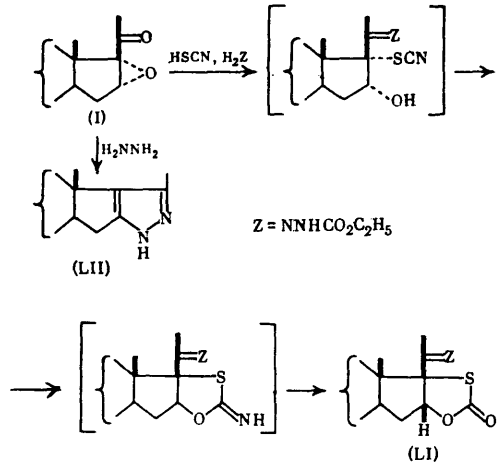


(XLVIII)
$Z = NNHCO_2C_2H_5$, X = O, S



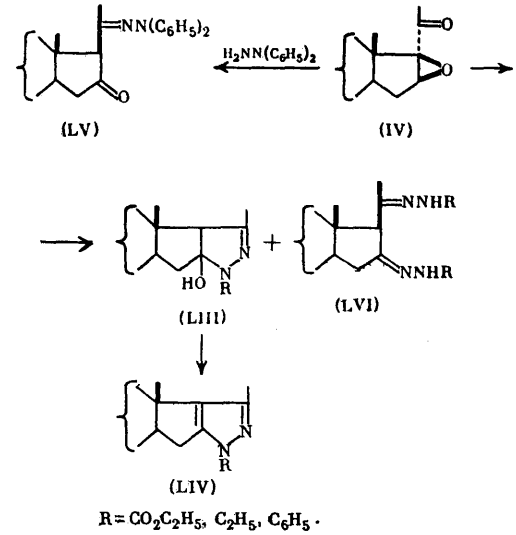
X = O (XLIX)
X = S (L).

The analogous reaction of the hydrazone (XLVIII) with thiocyanic acid yields the thiocarbonate (LI):



Exclusion of the nucleophilic reagent from the reaction medium directs the reaction of 20-hydrazones of 16,17α-epoxides towards cyclisation and formation of the pyrazole (LII).[83] This competes with the main reaction of (XLVIII) with thioacetic acid[72].

Incorporation of nucleophilic reagents is not observed in the ring-opening of 20-hydrazones of epimeric 16,17β-epoxides. Intramolecular cyclisation predominates, yielding the hydroxypyrazoline (LIII), which eliminates water to form the pyrazole (LIV):[78,79]

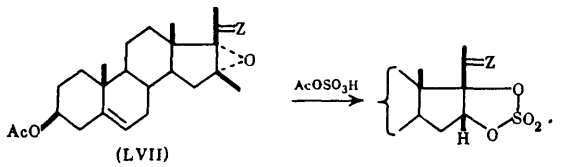


$R = CO_2C_2H_5$, C_2H_5, C_6H_5.

Use of diphenylhydrazine as reagent for a keto-group directs the process towards formation of a monohydrazone of the diketone (LV):[80,84] the second keto-group is not replaced by a hydrazone residue owing to steric hindrance. In several cases, e.g. in the presence of excess of ethyl hydrazinecarboxylate in acetolysis of the 16,17β-epoxide (IV), the dihydrazone (LVI) is formed together with the pyrazoline (LIII).[78] Complete elimination of deuterium in *cis*-ring-opening of the 16-deuterated 16,17β-oxide (IV) by acetic acid in dioxan indicates that these reactions occur with detachment of a proton from the $C_{(16)}$ atom and formation of the Δ^{16}-16-ol, which is then stabilised either by

intramolecular cyclisation involving the hydrazone fragment or by ketonisation[84].

The ditertiary 16β-methyl-16,17α-oxide (VIII) is an extremely interesting but little studied compound undergoing *cis*-ring-opening[46,98,99]. Both substituents adjacent to the epoxide, apparently involved in destabilising the carbocations formed when its ring opens, should promote cleavage of the epoxide bond in both directions. Nevertheless, the heterocycle in the epoxide hydrazone (LVII) is inert towards the ring-opening reactions of hydrolysis and acetolysis catalysed by mineral acids[98]. More severe conditions cannot be applied to the oxide 20-hydrazones owing to initial hydrolysis of the hydrazone group. Perhaps the only ring-opening reaction of the 16β-methyl oxide (LVII) that has been studied is the action of acetylsulphuric acid, which goes formally in the same direction as the corresponding reaction with the 16β-methyl-20-oxo-16,17α-oxide (VII):[46]



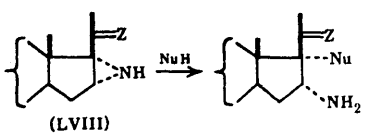
(LVII)

Z = $NNHCO_2C_2H_5$

2. *cis*-Ring-opening of 20-Hydrazones of 16,17α-Epi-imino-steroids

The synthetic aspect of *cis*-opening has been extended significantly to 16,17α-epi-imino-20-oxo-steroids[85-95,100,101]. They exhibit several general features—(*a*) high reactivity, exceeding by several times that observed for the epoxy-analogues, (*b*) addition of hydrazine at the keto-group in the stage preceeding ring-opening, (*c*) exclusive stereo- and regio-specificity of ring-opening at the position adjacent to the hydrazone fragment, and (*d*) occurrence under the reaction conditions of secondary cyclisation processes involving the 16,17α-*cis*-group formed—independently of the presence or absence of an *N*-substituent. A mechanism of *cis*-opening suggested for 16,17-epoxy-steroids has been extended to reactions involving 16,17α-epi-imino-ketones, and used to explain the changes observed[100].

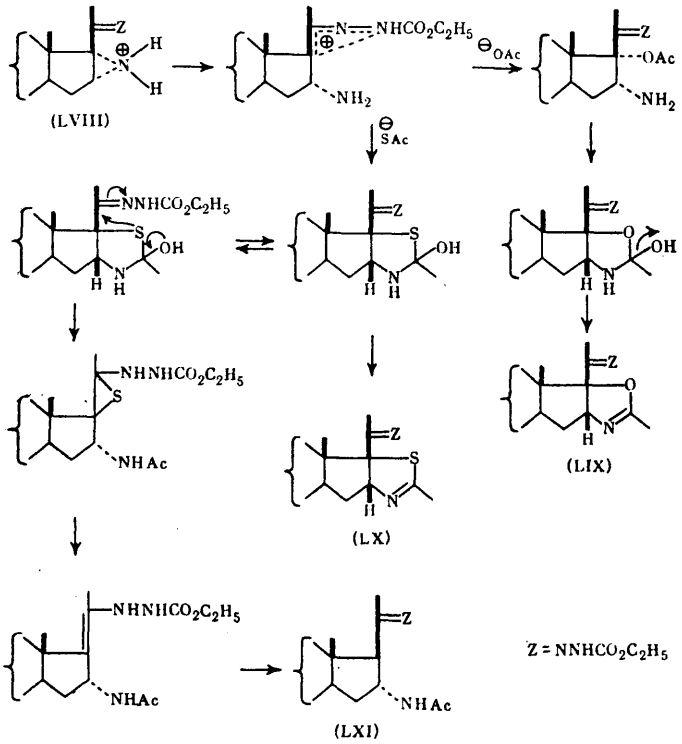
Exclusive incorporation of the nucleophilic reagent in the α-position to the hydrazone fragment from the rear of the molecule has been recorded in reactions of the 20-hydrazone (LVIII) with such reagents as hydrazoic acid[90,91,94], hydrogen fluoride[95], hydrogen chloride[88], water[87], and hydrogen sulphide[93], with formation of the 20-hydrazones of the corresponding products of *cis*-opening of the heterocycle:



(LVIII)

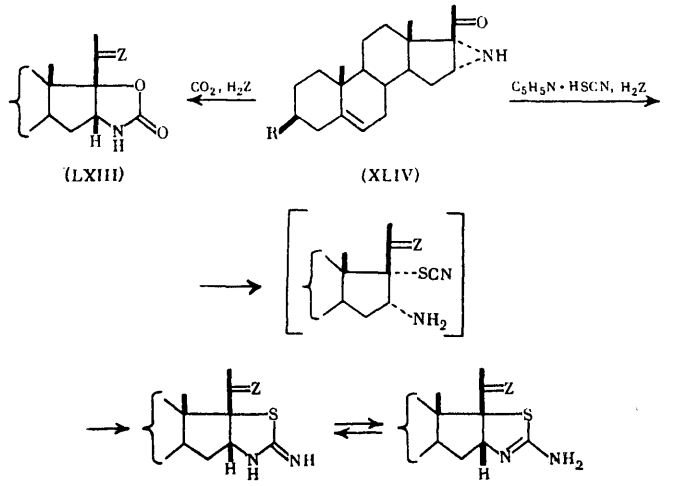
Z = $NNHCO_2C_2H_5$; Nu = N_3, F, OH, SH, Cl.

Attack by acetate (or *S*-thioacetate) ions at the $C_{(17)}$ atom in reactions of the epi-imine (LVIII) with acetic[85] and with thioacetic[86] acids is completed by cyclisation by the ortho-ester mechanism with formation respectively of the 2'-methyl-oxazoline (LIX) at the 2'-methylthiazoline (LX); water is eliminated at the stage of orthoester formation:



It is assumed that, in the action of thioacetic acid on the hydrazone (LVIII), stabilisation of the orthoester intermediate by intramolecular attack by sulphur at the $C_{(20)}$ atom in conformity with the above scheme leads to formation of the amide (LXI) as well as the thiazoline (LX).

Thiocyanic acid acts on the epi-imine (XLIV) to produce *cis*-ring-opening in the general direction, leading to incorporation of the thiocyanate ion in the vicinal position to the hydrazone group followed by cyclisation to a 2'-iminothiazolidine in tautomeric equilibrium with the 2'-aminothiazoline form (LXII):[86]

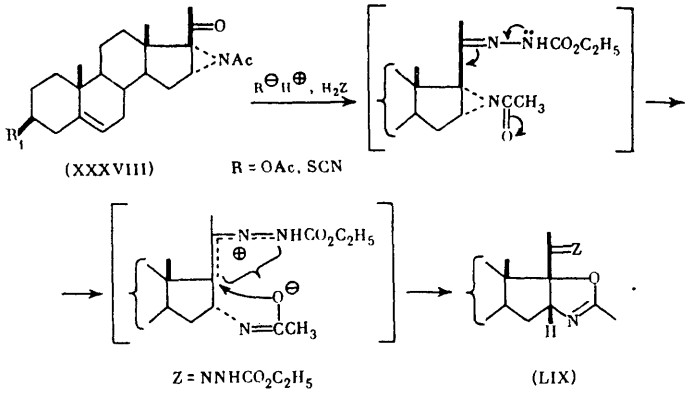


(LXII)

R = OH, OAc; Z = $NNHCO_2C_2H_5$.

The stereochemical requirements of reactions involving expansion of a three-membered to a five-membered ring suggest initial *trans*-opening followed by cyclisation, so that such reactions are atypical in polycyclic systems. It is interesting in this connection that the epi-imino-ketone (XLIV) reacts readily with carbon dioxide in the presence of ethyl hydrazinecarboxylate to form the oxazolidinone (LXIII): i.e. the favourable stereochemistry of ring-opening makes this process entirely feasible[101].

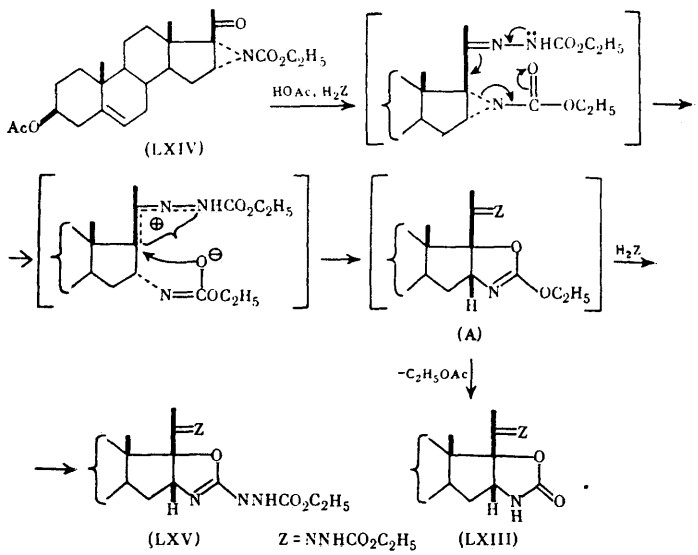
The general direction of ring-opening in *N*-substituted 16,17α-epi-imino-ketones in the presence of ethyl hydrazinecarboxylate does not differ fundamentally from that of their unsubstituted analogues, but stabilisation of the resulting 17-carbocation is effected not by incorporation of an external nucleophile but by intramolecular isomerisation involving an internal nucleophile. As a consequence, independently of whether an external nucleophile is or is not present, reaction with the *N*-acetylepi-imine (XXXVIII) results in formation of the oxazoline (LIX):



(XXXVIII) R = OAc, SCN

Z = $NNHCO_2C_2H_5$ (LIX)

The synthetic possibilities of the reaction can be extended by varying the *N*-substituent to obtain various new types of steroid heterocycles with a nitrogen atom attached to $C_{(16)}$. Thus formation of the oxazolidinone (LXIII) and its 2′-hydrazine derivative (LXV) in the reaction of the 16,17α-ethoxycarbonylepi-imine (LXIV) with ethyl hydrazinecarboxylate in acetic acid involves nucleophilic intramolecular cyclisation affecting the ethoxycarbonyl group[92,101]:



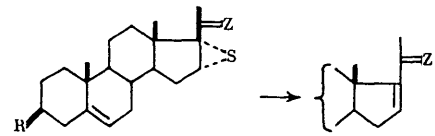
(LXIV) (A)

(LXV) Z = $NNHCO_2C_2H_5$ (LXIII)

It is assumed that the intermediate 2′-ethoxyoxazoline (A) reacts further by two independent paths: it either undergoes attack by the acetate anion with elimination of ethyl acetate or it condenses with a second molecule of ethyl hydrazinecarboxylate.

3. Opening of the Three-membered Ring in Ethoxycarbonylhydrazones of 16,17α-Epithio-steroids

Replacement of the oxo-group by a hydrazone fragment in 16,17α-epithio-20-oxo-steroids, in contrast to the above reactions of the 16,17α-epoxy(and epi-imino)-analogues, does not enhance the general reactivity of the episulphide ring. Moreover, the 20-ethoxycarbonylhydrazone of the 16,17α-epithio-ketone (LXVI) even exhibits some decrease in such reactivity, with an enhanced tendency to eliminate sulphur. It is sufficient to mention that, under the conditions of preparation (acetic acid and ethyl hydrazinecarboxylate at 20 °C), this hydrazone (LXVI) is converted partly—and to a greater extent with increase in exposure—into the alkene (LXVII):



(LXVI) (LXVII)

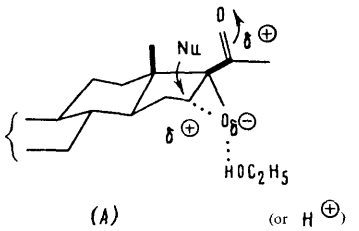
R = OH, OAc; Z = $NNHCO_2C_2H_5$.

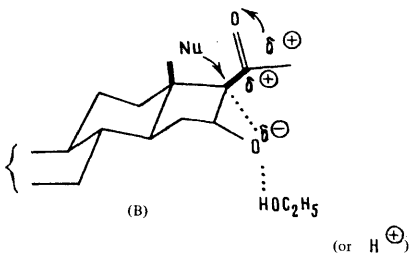
Reactions of the hydrazone (LXVI) have been studied with a wide range of reagents—water, methanol, acetic, thioacetic, and thiocyanic acids, the pyridine complexes of thiocyanic acid and of hydrogen fluoride, hydrazoic acid, ethanethiol, and phenylmethanethiol—but in no case has incorporation of the reagent been detected[96]. The reaction of the hydrazone (LXVI) with ethanethiol is exceptional: nuclear magnetic resonance spectroscopy and elementary analysis show that the chromatographically difficultly separable mixture of reaction products contains, together with the alkene (LXVII) and products formed by subsequent addition of the thiol to it, also a compound resulting from addition of the mercaptide ion to the episulphide ring.

VI. FACTORS CONTROLLING OPENING OF A THREE-MEMBERED RING

The above facts show that in these keto-oxides the classic *trans*-scission of the oxide ring at the β-position to the carbonyl group is most often (not always) evident only among 16,17α-epoxy-20-oxo-steroids. It appears useful to discuss the results systematised above in terms of a "borderline" or "modified" S_N2 substitution mechanism[3], which has become the most acceptable theoretical model for describing the opening of epoxide rings. According to this mechanism reaction between the oxide and a nucleophilic reagent involves a termolecular transition state, in which almost synchronous action of the nucleophilic reagent and an electrophilic "accomplice" (solvent or catalyst) causes rupture of a carbon–oxygen bond. The transition state of a "modified" reaction having an S_N2 mechanism has longer partial bond lengths than has the classic S_N2 mechanism, with rupture of the carbon–oxygen bond in the oxide always more pronounced than formation of the new carbon–nucleophile bond. This is evident in the appearance in the transition state of a partial positive charge on the carbon

atom of the reaction centre, the possibility of whose stabilisation determines the principal direction of ring-opening. Hence *trans*-opening of 16,17α-epoxy-20-oxo-steroids must be described in terms of the transition states





resulting from attack by the nucleophilic reagent from the front of the steroid molecule on the secondary and the tertiary centre respectively.

It can be assumed that transition state (A) is preferred not only because mutual repulsion between the two adjacent centres in (B) increases its activation energy[2] but also because the cationoid character of the $C_{(17)}$ centre in the latter is in some measure suppressed by the oxide ring in the preferred *S-trans*-conformation (Fig. 1*a*),[16,17,102] whose geometry satisfies the optimum requirements for conjugation of the keto-group with the oxide ring[7,12]. Furthermore, polar shielding by the neighbouring keto-function in the preferred conformation (*a*), and also the need for equatorial attack by the reagent in *trans*-opening of the oxide, do not favour realisation of transition state (B). The observed high stereo- and regio-selectivity of ring-opening reactions of 16,17α-epoxy-20-oxo-steroids with strong nucleophiles must then be explained by their occurrence via transition state (A), preference for which is due to concerted action of the conformational factor (*trans*-quasi-axial opening and attack from the opposite side of the oxide ring) and the electronic factor (electron-accepting influence of the keto-group when conjugated with the epoxide ring in the preferred *S-trans*-conformation).

Comparative analysis of steric factors in the intermediate species (A) and (B) does not support preference for either. Indeed, approach of the nucleophile to the $C_{(17)}$ and $C_{(16)}$ atoms is sterically hindered approximately equally by the angular and the $C_{(21)}$ methyl group in the *S-trans*-conformation, except that this involves respectively 1,3- and 1,2-interaction. This is why reactions with weak nucleophilic reagents take place in both directions, their result apparently depending on the relative rates of neutralisation of the two intermediate species. In particular, neutralisation of the carbocation centre at the $C_{(17)}$ atom by migration of the angular methyl group is more rapid than the alternative addition of a weak nucleophile (e.g. water) to the $C_{(16)}$ centre. In the absence of a nucleophilic reagent this becomes the sole reaction.

The geometry of ditertiary 16,17α-epoxy-16β-methyl-ketones differs from that of the desmethyl analogues. The preferred conformation of 16β-methyl-16,17α-epoxides is (*b*) (Fig. 1), in which the keto-group is oriented above the D ring in a skew position relative to the $C_{(13)}$–$C_{(17)}$ bond[17,102]. The general balance of steric and electronic factors changes in such a molecule (conjugation breaks down and the β-region of the molecule is strongly shielded), which by no means favours nucleophilic attack on the $C_{(16)}$ atom by an S_N2 mechanism. Therefore acid opening of the oxide ring in compounds of this type involves exclusively rupture of the $C_{(16)}$–O bond by a unimolecular mechanism with formation of a 16-carbocation, whose stabilisation is favoured by the 16-methyl group. Neutralisation is effected either by elimination of a neighbouring proton or by *cis*-opening of the oxide ring from the rear of the molecule[44].

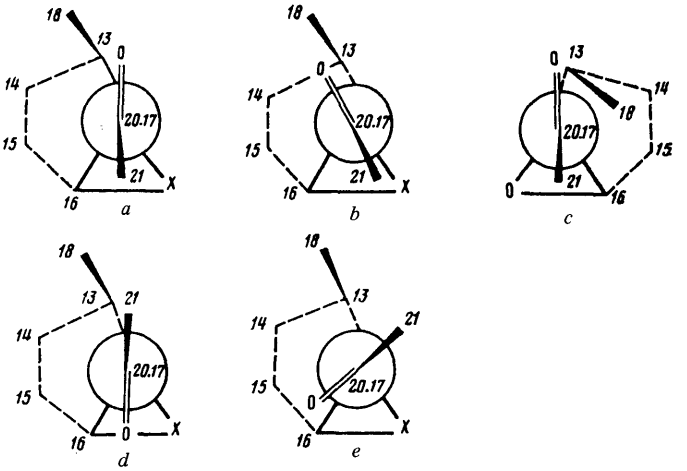
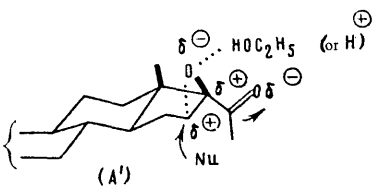
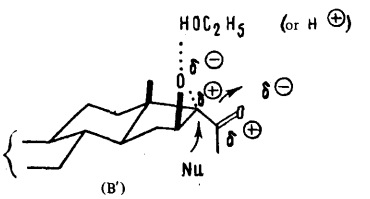


Figure 1. Newman projections of the conformations of 16,17-hetero-substituted 20-oxo-steroids, produced by rotation about the $C_{(17)}$–$C_{(20)}$ bond. The numerals denote carbon atoms.

In 16,17β-epoxy-20-oxo-steroids the general balance of factors controlling the structural direction and the stereochemistry of opening of the oxide is changed. Examination on the same basis of molecular models and of the intermediate states





shows that the total of factors promoting attack at the $C_{(16)}$ atom remains unchanged, whereas the number of factors opposing attack at the $C_{(17)}$ atom diminishes. The most important and apparently decisive difference between transition states (A') and (B') is that the conformational factor—*trans*-quasi-axial attack at the $C_{(17)}$ atom—promotes opening of the 16,17β-oxide at the tertiary $C_{(17)}$ atom. Furthermore, approach of the nucleophilic reagent to $C_{(17)}$ from the rear of the molecule is sterically less hindered in (B')§. The thermodynamic factor is favourable also to formation of products with a β-configuration of the 17-acetyl group on ring-opening of 16,17β-epoxy-20-ketones. All these considerations make *trans*-attack by the nucleophilic reagent at the tertiary centre in the opening of 16,17β-epoxy-ketones logically understandable, but it is difficult in the general logic of the argument to explain their *cis*-opening at this centre, and also the Wagner–Meerwein rearrangement. It can therefore be supposed that the transition state of carbocation type (B') formed in the modified S_N2 mechanism is characterised more by breakage of the old bond than by formation of a new bond, with consequent smaller steric hindrance to attack from the β-region.

Most of the ring-opening reactions of keto-aziridines, both basic (including protonated) and activated, are classified as substitutions, in which S_N2 and S_N1 mechanisms compete depending on the structure of the aziridine and the reagent[6]. The observed *trans*-stereochemistry of the opening of 16,17α-epi-imino-ketones and their *N*-acetates indicates reactions of type S_N2. This applies equally to those involving rupture of the $C_{(17)}$–N bond, for an S_N1 substitution would be expected to yield not only products of a Wagner–Meerwein rearrangement but also those of attack at the $C_{(17)}$ carbocation from the rear, less hindered side of the molecule. Differences in reactivity between 16,17α-epi-imino-ketones and their structurally similar epoxy-analogues must apparently be explained, in terms of an S_N2 substitution mechanism, by the difference in their geometry shown in the Newman projections in Fig.1.[15,17,102] The *S*-cisoid conformation (*d*) is assumed for the aziridine (XLIV), with the keto-group and the *N*-proton involved in an intramolecular hydrogen bond. In the preferred conformation of the *N*-acetylaziridine (XXXVIII) the keto-group is displaced from conjugation with the ring and skew to the $C_{(16)}$ centre inside ring D, with both acetyl groups *cis*-oriented with respect to the plane of the aziridine ring (Fig.1*e*). The lower reactivity of the aziridine (XLIV) in ring-opening involving the $C_{(16)}$ centre than of epoxides, and its tendency to isolated addition both at the keto-group and at the aziridine ring, are explained by the difference in conformation between the initial molecules and the consequent change in balance of steric and polar factors[102]. This provides an explanation also of the low reactivity of the *N*-acetates (XXXVIII), in which strong polar shielding by the two carbonyl functions of the acetyl groups prevents approach of a nucleophilic reagent to the $C_{(16)}$ atom.

Epithio-ketones are far less reactive than their oxygen analogues, but still show a tendency to the same direction of ring-opening. The episulphide (XLVI) is a conformationally more labile model than the epoxy-analogues, but the conformational mobility of the 17β-acetyl group is restricted to conformations having *trans*-orientation of the keto-group and the heterocycle, with the *S-trans*-conformation (Fig.1*a*) showing minimum energy, and 30° deflection of the 21-methyl group towards coplanarity of the keto-group and the $C_{(17)}$–S bond energetically preferred to displacement in the opposite direction[103,104]. The factor stabilising the system in the preferred *trans*-conformation is apparently orbital interaction of the carbonyl with the delocalised electronic system of the episulphide ring. The difference in character between this interaction in the episulphide (XLVI) and in the epoxide (I) is evident from Fig.2, which illustrates the distribution of electron density obtained by quantum-chemical calculation in the energetically preferred conformations of the ground state of a fragment of the D-ring in (I) and (XLVI) with an indication of the bond lengths determined by X-ray structural analysis[16,103,104]. The episulphide shows diminished electrophilicity of the carbon centres at the points of attack and also diminished polarisation of its keto-group, the latter obviously due to displacement of the electron shell from the carbonyl group to a vacant *d*-orbital of the sulphur atom[105–107]. It may be supposed that these electronic differences together with the establishment of a conformation sterically favourable for elimination of sulphur, with anti-coplanar arrangement of keto-group and $C_{(17)}$–S bond, are responsible for the above behaviour of the episulphide in ring-opening reactions.

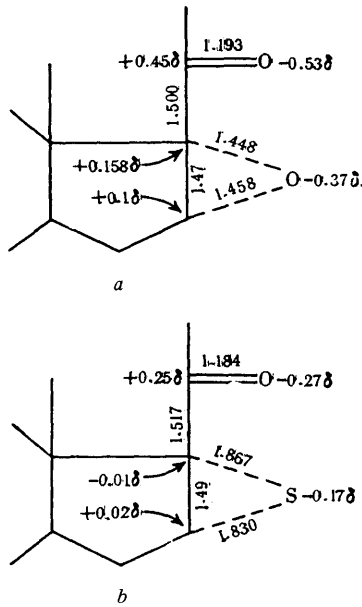
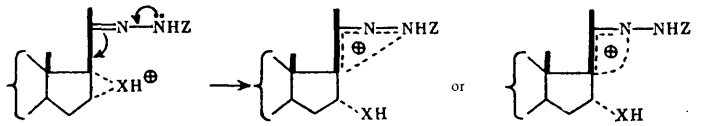


Figure 2. Distribution of electron density on atoms of the D-ring obtained by quantum-chemical calculation and interatomic distances (Å) determined by X-ray structural analysis for the: *a*) epoxide (I); *b*) episulphide (XLVI).

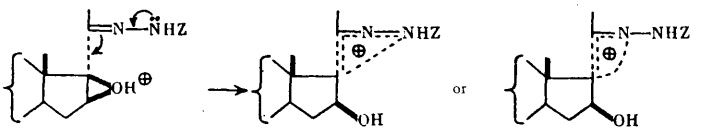
§By analogy with 16,17α-epoxides the preferred conformation of 16,17β-epoxy-20-oxo-steroids is taken to be (c) (Fig.1), with *anti*-orientation of the oxygen functions (oxo- and epoxy-groups).

Replacement of the keto-group by a hydrazone fragment apparently reverses completely the direction of polarisation of the system[63]. Under acid conditions reversible electronic displacement of the lone pair of the amino-nitrogen atom along the conjugated chain becomes more characteristic,

with a consequent loosening of the heterocyclic $C_{(17)}$–X bond (X = O, NH, $NCOCH_3$). At present, unfortunately, experimental information on the mutual steric arrangement of hydrazone group and three-membered ring is lacking. However, the fact that the configuration at $C_{(17)}$ is strictly maintained indicates rather preference for the *S*-transoid conformation. On the basis of the experimental facts it is suggested as intermediate species a non-classical cyclic ion stabilised in the configuration of the initial oxide or aziridine hydrazone:



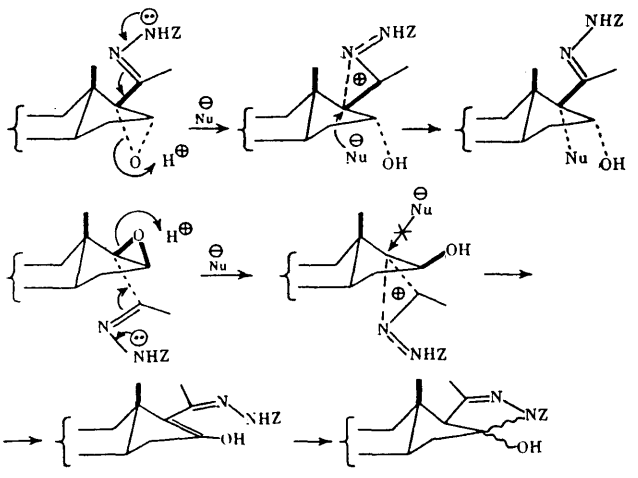
X = O (XLVIII)
X = NH (LVIII)
X = NAc



Z = $CO_2C_2H_5$.

The question of whether both hydrazone nitrogen atoms are involved in this interaction or only that closer to the ring remains open[63].

Two factors—presence of a nucleophilic reagent and possibility of its approach to one side or the other of the non-classic cation—govern the subsequent fate of the latter. In the 20-hydrazone of the 16,17α-oxide the configuration of the cation requires approach of the reagent from the rear of the molecule. As a consequence, in the presence of a nucleophile the reaction is completed by its incorporation at $C_{(17)}$, and in the absence of such a reagent by elimination of a proton from the $C_{(16)}$ atom followed by intramolecular cyclisation involving the hydrazone fragment:



Z = $CO_2C_2H_5$, C_6H_5.

The reason for the observed course of the reaction in the latter case is the impossibility of any other way of satisfying the electronic requirements of neutralisation of the non-classical cation. The configuration of the cation of the 16,17β-epoxide 20-hydrazone requires that a nucleophile should attack from the side of the sterically-shielded β-region of the molecule. As a consequence, its neutralisation is effected not by addition of the nucleophile from the side of the β-epoxy-group but by elimination of a neighbouring proton with formation of a Δ^{16}-enol, which either rearranges into a ketone or cyclises into a pyrazolinol. But the latter role in the general direction of ring-opening reactions of oxide 20-hydrazones is apparently played by the geometrical arrangement of the hydrazone fragment relative to the plane of the three-membered ring, although this aspect has remained almost uninvestigated.

The anomalous behaviour of the 20-hydrazone of the 16,17α-epithio-ketone (LXVI) in ring-opening reactions suggests a different mechanism of interaction of the episulphide ring and the hydrazone fragment, without formation of an intermediate non-classical carbocation.

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